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Hearing outcomes in children with Congenital Cytomegalovirus: A multi-center, single-enterprise experience

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ABSTRACT

Background: Cytomegalovirus (CMV) is the most common cause of non-genetic sensorineural hearing loss (SNHL) in the United States; yet screening for congenital CMV (cCMV) remains controversial. CMV related SNHL can be present at birth, or develop in a delayed manner, and it is a consistent feature in children with either symptomatic or asymptomatic disease. A retrospective chart review was performed to determine the characteristics of patients diagnosed with cCMV and SNHL.

Methods: The electronic database warehouse of the Nemours Children's Health System (NCHS) was queried from 01/01/2004 to 10/05/2019. ICD 9 (771.1) and ICD 10 (B25.9, P35.1) diagnostic codes were used to identify patients throughout the system with a diagnosis of cCMV infection. Patient demographics including gender, race/ethnicity, age of diagnosis, results of newborn hearing screening (NBHS), detection and progression of hearing loss, presence of antiviral therapy, and frequency of monitoring were collected, and descriptive statistics performed.

Results: Of the 170 patients confirmed to have cCMV, 153 (90%) were symptomatic and 17 (10%) were asymptomatic. CNS involvement (63.5%), radiographic evidence of disease present (69.4%), and SNHL (50.6%) were the most common manifestations of the disease. Of these 170 patients, 83 (48.8%) were determined to have SNHL eligible for evaluation. For these patients with SNHL, the average time of hearing monitoring was 50.6 months. At the time of initial reported detection 63 of 83 (76%) had bilateral hearing loss and 20 (24%) had unilateral loss. Over the study period 3 (15%) progressed from unilateral to bilateral involvement, and 32 (47%) had a deterioration in hearing, with severe to profound SNHL in at least one ear identified at the last visit in 53 (64%) patients. Newborn hearing testing results were available for 69 (83%) of those with hearing loss and 26 patients passed initial testing. However, of the 26 patients who passed, 22 (85%) eventually developed SNHL by their last visit. Within our cohort, females with cCMV were significantly more likely to have SNHL than males with cCMV (62.3% versus 37.6%; $p < 0.01$).

Conclusion: In the absence of targeted or universal cCMV screening, the majority of children identified with this condition present symptomatically. Approximately one half of children with symptomatic cCMV failed NBHS at birth while at least 25% develop SNHL later in life. Children with cCMV are at high risk of delayed onset loss and such children, particularly females, should be monitored closely.

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1. Background

Cytomegalovirus (CMV) is the most common congenital infection worldwide and the most common cause of non-genetic sensorineural hearing loss (SNHL) in the United States [1]. Congenital Cytomegalovirus (cCMV) affects six to seven newborns per 1000 in developed countries and ten to fifty per 1000 live births in developing countries [2].

The presentation of cCMV varies widely between mild nonspecific findings to multi organ system involvement and death. The virus affects the reticuloendothelial and central nervous systems. Approximately 10–15% of cCMV patients present symptomatically with sequelae such as petechiae, jaundice, and microcephaly. However, 85–90% of cCMV patients present asymptomatically, though they remain at risk for developing hearing loss [3,4].

In a large longitudinal study, Dahle et al., 2000 found that about 40.7% of symptomatic cCMV patients develop SNHL with a median detection of 33 months, whereas 7.4% of asymptomatic cCMV patients develop SNHL with a median detection of 44 months [5]. Fowler et al., 1997 found that 18.2% of cCMV patients (with asymptomatic cCMV only) have delayed onset SNHL with further deterioration of hearing occurring in 50% of them. The hearing loss varies widely in severity from mild to profound and may be unilateral or bilateral in nature. The hearing loss will fluctuate in 22.7% of infections [6]. There is greater severity of loss in symptomatic children, and they are more likely to present with bilateral hearing loss than asymptomatic children [7,8].

Approximately 10% of neonates with congenital CMV are symptomatic at birth [9]. SNHL is present at birth in 35% of symptomatic patients but presents with a delayed onset in 18–30% of cases [8,10–12]. SNHL is present in 33–50% of all symptomatic cCMV patients [8,10–12]. Hearing loss is bilateral in 71% of symptomatic patients compared with 43% of asymptomatic patients [8]. In symptomatic patients, the hearing loss is progressive in 18–63% of patients with 78% of affected ears eventually becoming severe to profound [8,10,11]. Microcephaly is present in 35–50%, petechiae in 50–75%, and hepatosplenomegaly in 40–60% [10,13,14]. Common lab abnormalities such as thrombocytopenia and elevated transaminases are present in 48–77% and 50–83% of symptomatic patients respectively [10,13,14].

This leaves an estimated 90% of congenital CMV patients thought to present asymptomatically. Slightly lower birth rate and gestational age are observed in these symptomatic infants [10]. Ten to 15% of asymptomatic cCMV patients experience SNHL [6,8]. Ten to 15% of these patients experience hearing loss in infancy and early childhood with up to 25% experiencing SNHL by age 18 years [6,8,15–17]. Asymptomatic patients are less likely to have bilateral severe to profound hearing loss than symptomatic patients (43 versus 65%) [8]. The two groups have similar rates of progressive hearing loss (20%) and fluctuating hearing loss (20–25%) [8]. In a study of 92 infants with asymptomatic cCMV, 22% developed SNHL over a median follow-up period of 17 years [18]. In a study of 572 newborns who failed NBHS, 6% were found to have cCMV with 75% of these infants with cCMV identified solely on the basis of their abnormal hearing screening [19]. Radiographic evidence of cCMV has been identified in 5–20% of otherwise asymptomatic infants [10].

The pathogenesis of CMV-related hearing loss is not well understood, although there are theories that direct cytopathic effects, localized inflammatory responses and vascular injury may play a role. Others hypothesize that direct fetal injury may be induced by pathologic virally encoded gene products as these products function at the RNA and protein level to interfere with cellular processes. Downstream effects of this disruption include modification of the cell cycle, interference with apoptosis, induction of an inflammatory response, and facilitation of evasion of host immune responses [20,21]. There is also evidence to suggest the unique presentation of delayed hearing loss may be associated with persistent CMV shedding during childhood, particularly localized CMV shedding in the ear [22].

Unlike other etiologies of congenital hearing loss, there is some evidence which suggests improvement in hearing and neurodevelopmental outcomes with six months of antiviral treatment rather than six weeks of antiviral treatment [2,23]. Given these realities, there is growing support for routine screening for CMV in newborns. This multi-center, retrospective cohort analysis of pediatric patients with cCMV aimed to examine and characterize demographical data, clinical symptoms, and hearing outcomes in children over time and add to the growing body of knowledge on this patient population. We anticipated in this historical cohort the majority of children with cCMV would be characterized as having symptomatic CMV and the associated hearing loss would be largely bilateral.

2. Methods

This project was approved by the Nemours Institutional Review Board 2 in Jacksonville, FL on 10/15/2019 with study number 1507322-6. Using the electronic database warehouse of Nemours Children's Health System, individuals between 01/01/2004 to 10/05/2019 with diagnosis of CMV using ICD 9 (771.1) and ICD 10 (B25.9, P35.1) were identified. Individuals with the specific diagnosis of congenital Cytomegalovirus were then identified by using the search terms "CMV," "congenital," and "cytomegalovirus." Chart review was performed to identify individuals with cCMV by using the presence of laboratory or strong clinical evidence of disease categorization based on the perceived accuracy of diagnosis assigned. Patients were categorized based on documentation and grouped into one of the four categories of cCMV disease as proposed by the International Congenital Cytomegalovirus Recommendations Group 2015 and Kimberlin et al. [23,24]. The category of CMV was identified based on number of symptoms present. If the patient had three or more symptoms, they would be characterized as a category four. If the patient had two symptoms, there were characterized as a category three. If the patient solely had hearing loss and no other symptoms, they were characterized as a category two. If the patient was completely asymptomatic, they were characterized as a category one. In determining those with symptomatic disease, the following clinical characteristics were considered: gestational age at birth, less than three months at diagnosis, age at cCMV diagnosis, method of diagnosis, thrombocytopenia, petechiae, hepatomegaly, splenomegaly, intrauterine growth restriction (IUGR), transaminitis, central nervous system (CNS) involvement, microcephaly, chorioretinitis, radiographic evidence of CMV, CMV in cerebrospinal fluid (CSF), SNHL, and presence of antiviral therapy at birth. Symptoms were deemed present if documented at any time in their life not determined to be due to any other cause than cCMV infection. CNS involvement was defined by the presence of two or more of the following: microcephaly, chorioretinis, CMV in CSF, or radiographic evidence of CMV manifestations in the CNS. Further, if the patient saw neurology for developmental disorders, seizures, or other neurological dysfunction documented at any time in their life as a result of cCMV infection, this was sufficient for presence of CNS involvement. Radiographic evidence of CMV was present if any of the following were documented: ventriculomegaly, hemorrhages, or calcifications. Usually, this evidence would be found on brain ultrasound, CT scan, or MRI, but if found on the liver (i.e. "liver calcifications") this was also sufficient evidence for presence of radiographic evidence of CMV.

Demographics including gender, race/ethnicity, age of diagnosis, and results of NBHS were collected. Detection and progression of hearing loss and frequency of monitoring was collected, with descriptive statistics performed. Degree of hearing loss was characterized as profound, severe, moderate, mild, slight, normal, or unknown. Hearing loss laterality, date of diagnosis, degree of hearing loss at detection, degree of hearing loss at most recent visit, and most recent visit date were noted. For ease of data analysis, the most advanced degree of hearing loss was included (i.e. "moderate to severe" hearing loss would be considered "severe").

Chi squared tests were performed to determine significance. Tests for

statistical significance were performed and analyzed using IBM SPSS 25.0 software. For a significance parameter for these tests, a p-value of 0.05 was used.

3. Results

A total of 872 patients from the NCHS warehouse were first identified. 202 patients were excluded with documentation to indicate the child did not carry the CMV diagnosis. From the remaining 670 patients, 466 were excluded with documentation to indicate the child had a CMV transplant infection rather than a cCMV diagnosis. The remaining 204 patients were reported to have cCMV diagnosis. However, only 170 patients were found to have true cCMV diagnosis based on the following criteria. One hundred and seventeen patients were confirmed to have diagnosis of cCMV based on laboratory data (detection of CMV DNA in the urine, saliva, or blood) collected within the first three months of life, and another 53 patients were included after close review of medical records identified the diagnosis of cCMV within the first three months of life. Thirty-four patients had documented evidence against cCMV or no evidence of cCMV based on negative urine tests or positive laboratory tests past three months of age and were excluded (Fig. 1). Table 1 displays the demographic information of this cohort with the confirmed diagnosis of cCMV.

Among the 170 identified cCMV cases, 145 (85%) were diagnosed with cCMV in the first month of life (69% at birth, 7% prenatally, and 24% at some other time within the first month of life), 5% were diagnosed past the first month of life, and the time of diagnosis for the remaining 10% was unknown. Nearly all patients (96%) were identified as symptomatic cCMV (Table 2). CNS involvement (63.5%), radiographic evidence of disease present (69.4%), and SNHL (50.6%) were the most common manifestations of the disease (Table 3).

Within the 170 patients, 105 were noted to have SNHL per medical record. Of these 105 patients, 83 were ultimately included in the study; 12 excluded due to inadequate data to determine if SNHL was truly present (i.e. no objective measure of hearing), three excluded for coexistent auditory neuropathy, and seven excluded who had normal hearing. Table 4 displays the demographic information of this cohort with confirmed SNHL.

In these 83 patients with confirmed SNHL, the time interval of hearing monitoring was <12 months in 25 (30%) children, one to five years in 33 children (40%) and > five years in 25 children (30%). Median time to detection (age at which hearing loss diagnosed or identified in system) was 8 months and interquartile range was two to 50.5 months. At time of detection 63 of the 83 children with SNHL (76%) presented with bilateral hearing loss (the SNHL was symmetric for 37 children, asymmetric for 18 and unknown for eight) and 20 (24%) had unilateral loss. At last visit (time at most recent testing), 66 children (80%) had bilateral SNHL (45 symmetric, 17 asymmetric and four unknown) and 17 children (20%) had unilateral losses. Over the monitoring period, three (15%) out of the 20 children with unilateral SNHL progressed from a unilateral to a bilateral involvement. After excluding those with profound hearing loss at detection, 32 children out of 68 (47%) had a deterioration in hearing. Severe to profound SNHL was present at the last visit in 53 (64%) patients; – 13 (25%) with unilateral loss, 39 (74%) with symmetric bilateral losses, and 1 (1%) of unknown laterality). The majority of patients (75%) received newborn hearing screening (NBHS), though the type of test(s) used for the screening was unknown (otoacoustic emissions and/or automated auditory brainstem

Table 1
Demographic information of cCMV patients.

Gender	
Male	93 (54.7%)
Female	77 (45.3%)
Race	
Caucasian	95 (55.9%)
African American	52 (30.6%)
Asian	3 (1.8%)
Not reported	20 (11.7%)
Ethnicity	
Hispanic	24 (14.1%)
Non-Hispanic	146 (85.9%)

Table 2
cCMV patients identified by category.

Category of cCMV	Category	Number of Patients	Percentage of cCMV Patients
1	Completely asymptomatic	6	3.5%
2	Asymptomatic and hearing loss only	11	6.5%
3	Mildly symptomatic (1–2 symptoms)	35	20.6%
4	Moderate-severely symptomatic (2–3 symptoms)	118	69.4%

Table 3
Symptoms identified in cCMV patients.

Symptom	Yes	No	Unknown
Thrombocytopenia	70 (41.2%)	62 (36.5%)	38 (22.4%)
Petechiae	41 (24.1%)	99 (58.2%)	30 (17.6%)
Hepatomegaly	31 (18.2%)	129 (75.9%)	10 (5.9%)
Splenomegaly	31 (18.2%)	129 (75.9%)	10 (5.9%)
IUGR	50 (29.4%)	5 (2.9%)	115 (67.6%)
Transaminitis/Hepatitis	59 (34.7%)	58 (34.1%)	53 (31.2%)
CNS Involvement	108 (63.5%)	40 (23.6%)	22 (13.0%)
Microcephaly	80 (47.1%)	80 (47.0%)	10 (5.9%)
Chorioretinitis	16 (9.4%)	143 (84.1%)	11 (6.5%)
Radiographic Evidence	118 (69.4%)	35 (20.6%)	17 (10.0%)
CMV in CSF	5 (2.9%)	11 (6.5%)	154 (90.6%)
SNHL	86 (50.6%)	65 (38.2%)	19 (11.2%)

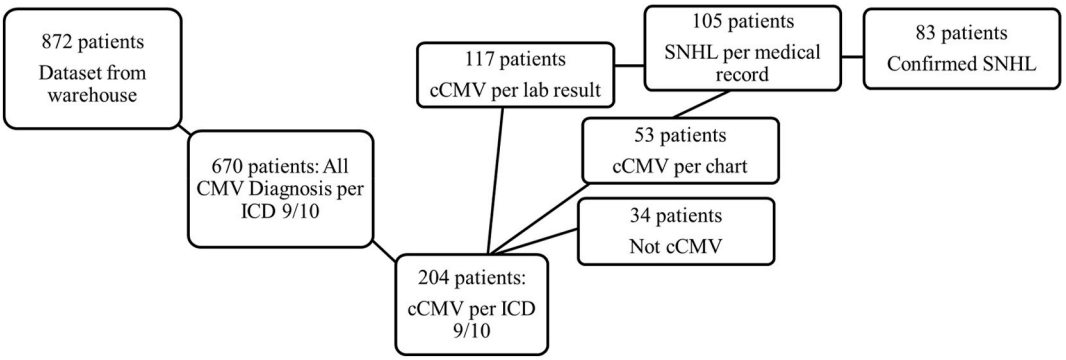

Fig. 1. cCMV chart review methodology.

Table 4
Demographic information of SNHL patients.

Gender	
Male	35 (42.2%)
Female	48 (57.8%)
Race	
Caucasian	54 (65.0%)
African American	20 (24.1%)
Asian	0 (0%)
Not reported	9 (10.9%)
Ethnicity	
Hispanic	16 (19.3%)
Non-Hispanic	67 (80.7%)

response). Ninety three percent of the time this was performed within the first month of life. In the 83 patients with a confirmed diagnosis of cCMV, the NBHS data revealed that 43 failed, and 26 passed (NBHS status was unknown in 14 patients). Of the 26 reported to have passed their NBHS, ten (39%) were found to have a unilateral loss at the time of first detection (the initial visit since originally being screened), 12 (46%) had bilateral loss, and 4 (15%) had no loss. Two of the ten unilateral losses converted to bilateral losses by last visit. Using this available data in our cohort of symptomatic cCMV child with who eventually developed SNHL, 85% of those who passed their NBHS subsequently developed SNHL by their first detection (Fig. 2).

In children with symptomatic, cCMV bilateral SNHL (63 patients) was more likely to occur than unilateral SNHL (20 patients), ($p < 0.01$). Hearing loss progressed in severity in 80% of patients with unilateral loss and 56% with bilateral loss after those with profound hearing loss at detection were excluded. Children with symptomatic cCMV were more likely to experience progression of severity of hearing loss in a statistically significant manner in unilateral vs bilateral SNHL ($p = 0.012$). Hearing loss improved in 12% of patients, which was defined as a reduction in degree of hearing loss from detection to the last visit in at least one ear with no deterioration of hearing in any ear. Within our cohort, females with cCMV were significantly more likely to have SNHL than males with cCMV (62.3% versus 37.6%; $p < 0.01$). Otherwise, there were no statistically significant differences in incidence of SNHL, CNS involvement, or radiographic evidence of disease between race/ethnicity or gender.

Nearly equal number of patients received antiviral treatment; 43 with treatment and 47 without treatment, yet no statistically significant difference was found in progression of the severity of hearing loss in at least one ear between the groups, antiviral therapy (38.5% antiviral intervention group vs 53.1% non-antiviral intervention group; $p = 0.152$). Interestingly, none of the antiviral therapy patients progressed to bilateral hearing loss, whereas three of the patients in the non-antiviral intervention group progressed to bilateral hearing loss, though this again was not statistically significant ($p = 0.339$).

4. Discussion

4.1. Prevalence of SNHL in cCMV

Cytomegalovirus remains a significant cause of morbidity, especially SNHL in infants and young children. It has been reported 3–5% of all children with cCMV are estimated to develop bilateral moderate to profound SNHL [25]. Among the general population of children with bilateral moderate to profound SNHL, it is estimated 15–20% are attributable to cCMV [25].

Our study pooled data from a multi-center pediatric enterprise to characterize the outcomes in children with (largely symptomatic) congenital CMV. Overall, our findings support previously published data on prevalence of hearing loss in symptomatic cCMV children, though some differences exist. In our cohort approximately 53% of children with cCMV developed SNHL, consistent with the 22–65% reported in the literature [15]. We report 80% of patients possessing bilateral SNHL, a finding also consistent with the published reports [26,27]. The 46% of symptomatic children developing SNHL in our cohort was not surprising, and once again is consistent with the historical figures, such as the 40.7% reported by Dahle et al., in 2000 [5]. However, our data for asymptomatic patients with SNHL differ considerably from Dahle et al., as we report 41% of asymptomatic patients versus only 7.4% in their study. Other studies support this reporting a significantly higher prevalence of CMV-induced hearing loss in symptomatic than asymptomatic children [15,25]. We attribute this discrepancy to the very low presence of asymptomatic patients in our study. Our cohort was heavily skewed toward symptomatic patients—90% versus 10–15% of all cCMV patients in larger population studies [25,26]. This finding reflects the inability to capture otherwise asymptomatic cases without hearing targeted or universal screening, and hence supports the premise that without such a systematic approach to cCMV identification numerous children will go undiagnosed. Of note neurologic and radiological sequelae were seen in almost 65% and 70% of our cohort respectively, a finding almost consistent with the 81% seen in the published literature [27], despite the lack of information in several of our patients.

The prevalence of severe to profound bilateral SNHL is shown to be 2% in asymptomatic patients [16]. In our cohort, 29.4% of asymptomatic patients were found to have severe to profound bilateral SNHL. The discrepancy in our cohort is most likely due to our inability to identify a larger population of asymptomatic cCMV patients.

In Bilavsky et al., hearing impairment in patients with symptomatic cCMV was found in 36.2% at birth, with 57.4% being unilateral and 42.6% being bilateral [28]. Our cohort found 28.1% with hearing impairment at birth, with 24% having unilateral and 76% having bilateral hearing loss.

4.2. Progression of hearing loss in cCMV

Many studies have attempted to characterize the progression of SNHL in cCMV patients, but results were highly variable. It is

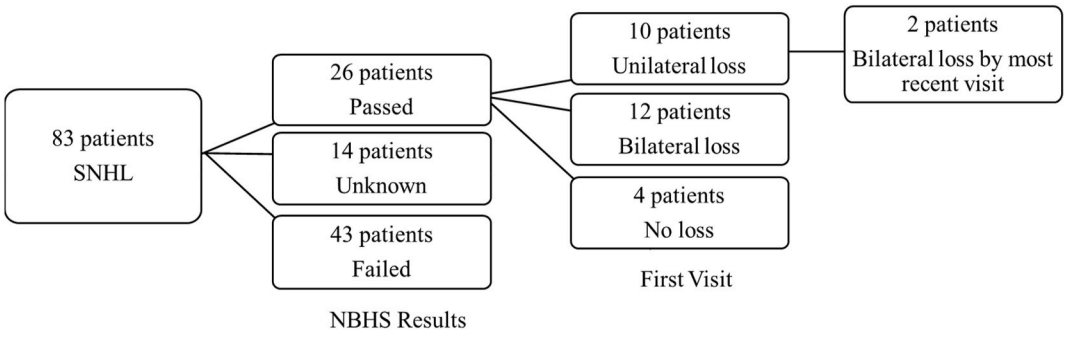

Fig. 2. Progression of hearing loss in cCMV patients.

challenging to predict which children will develop hearing loss and if the loss will be progressive. Progression can refer to sidedness (unilateral to bilateral) or severity (mild to profound). Studies support this reporting a significantly higher prevalence of cCMV-induced hearing loss in symptomatic than asymptomatic children with the formers also significantly more likely to develop bilateral hearing loss [25–27,29]. In 1997 Fowler et al. [6] reported 50% of asymptomatic cCMV patients had a deterioration in their hearing while 37.5% of the asymptomatic cCMV patients in our cohort experienced deterioration. However, we accept these numbers are difficult to extrapolate as our cohort of asymptomatic patients is quite small. Only eight of the asymptomatic patients in our cohort were found to have true SNHL in at least one ear. In 2005, Madden et al. [27] reported 43% of symptomatic cCMV patients had a deterioration in their hearing while in 2017 Fowler et al. [30] reported 50% of symptomatic cCMV patients experienced deterioration. We report a comparable 47% of the symptomatic cCMV patients in our cohort experienced a deterioration in hearing. It should be recognized that meta-analyses have found a significant heterogeneity in studies reporting deterioration in hearing among asymptomatic and symptomatic cCMV patients, and while this necessitates caution in comparisons between studies it also highlights the challenge associated with predicting whether the child will experience progressive hearing loss [20,31].

The effect of antiviral medications on the progression of hearing loss has been explored in the literature [23], and physicians should consider this treatment option in qualifying neonates. Royackers et al., presented a cohort of 27 symptomatic children with unilateral or bilateral hearing loss. In the group treated with ganciclovir, 37.5% of the children had stable hearing loss, 37.5% had improvement of hearing threshold, and 12.5% had deterioration in hearing. Among the untreated children, hearing loss was stable in 50% and deterioration occurred in 37.5% with 2.2% progressing from unilateral to bilateral hearing loss [29]. Our therapy group was treated with ganciclovir. In our cohort, 39.5% (17/43) of the therapy group and 53.1% (25/47) of the nontherapy group had worsening severity of hearing loss in at least one ear; 6.4% (3/47) of the nontherapy group progressed from unilateral to bilateral hearing loss. While we discovered a higher deterioration rate in the nontherapy group, this did not reach statistical significance, and the rate of deterioration our antiviral therapy group is considerably higher that what has been published. These discrepancies are likely due to the following. Our cohort was three times the size of Royakers et al.'s and may reflect a greater discrepancy between those treated with ganciclovir and those without. Royakers et al. presented a prospective study following patients for six years while ours was retrospective with patients followed over various time periods. Therefore, the age at treatment onset, dosage, and length of treatment were not standardized compared to Royackers et al. Furthermore, Royackers et al. presented results which did not exclude patients with baseline profound hearing loss as was done in our study. This may have had greater implications in their smaller cohort. Changes in hearing loss were defined as an increase or decrease in hearing of greater than 10 dB in Royackers et al., whereas our study defined changes in hearing by degree of hearing loss [29].

Progression from unilateral to bilateral hearing loss is a known attribute of CMV related hearing loss. Although the characterization of unilateral and bilateral hearing loss in patients with cCMV is recognized, data discussing progression from unilateral to bilateral is more limited. What is in the literature identifies 7.5% of unilateral hearing loss progressing to bilateral loss. cCMV infection was confirmed in 10% of the unilateral hearing loss cases [32]. The limited data may be a result of small populations progressing in this manner or an inability to capture this progression over time. Nonetheless, this is a gap in the literature for future exploration.

The timeliness of audiological evaluation in patients with symptomatic cCMV infection is important even when these patients pass their NBHS. In our group, for children ultimately developing SNHL, 85% of those passing NBHS developed SNHL. In Kim et al., almost 42% of ears with hearing loss were diagnosed after a passed NBHS [33]. In CHIMES study, 43% of hearing loss developed after a passed NBHS, and as mentioned earlier such consequential realities highlight the limitation of a hearing targeted screening program and lend support to the cause of universal CMV neonatal testing [30].

These results may be affected by the duration of observation of our cohort. The wide range of duration from less than 12 months to more than five years is due to loss to follow up and differences in patient age.

4.3. Universal screening for cCMV

Universal screening is controversial, yet our study supports the growing body of literature clearly demonstrating targeted testing is inadequate. Targeted CMV testing of newborns after a failed NBHS has identified the majority of cCMV related hearing loss. However, 43% of infants with cCMV related hearing loss in the neonatal period were not identified by NBHS [30]. Methods for targeted testing include not only failed newborn hearing screening, NICU admission, coexistent maternal HIV infection, yet collectively they would miss otherwise asymptomatic children who once infected are at risk for hearing loss, consequential language delay, and educational inadequacies with challenges. If delayed onset hearing loss is this prevalent in symptomatic who we have some reason to suspect CMV, shouldn't we be concerned about the asymptomatic child when disease is hidden, but risk of development of hearing loss is real and measurable.

As of January 2022, CMV legislation has been effectively passed in 13 states in the United States. Six of these states have targeted CMV testing; however, Minnesota has become the first state to enact universal newborn CMV screening [34]. The feasibility and cost benefit analyses for universal screening is still scrutinized. Cost comparisons in Australia for salivary CMV PCR tests have been shown to be negligible, indicating universal screening is feasible [35,36]. Other studies have argued cCMV is too rare to implement universal screening programs [37,38]. Earlier studies found as much as 23–33% of patients who presented with symptomatic cCMV passed their NBHS [39–41]. Fowler et al., estimates 50% of asymptomatic cCMV patients pass and found 43% of symptomatic cCMV patients pass their NBHS. This provides evidence to support approximately half of both symptomatic and asymptomatic cCMV patients are missed by NBHS. However, more evidence to support these claims is required. Fowler et al., speculated these numbers may be higher because hearing loss occurred after the first week after birth or progressed to a measurable level by six to eight weeks after birth [30]. The discrepancy in our results may be due to the heavily skewed cohort in favor of symptomatic patients. Cushing et al. estimates 60% of children who developed SNHL did so by two and a half years and 80% by five years. Furthermore, in children who passed their NBHS in one or both ears, 50% developed hearing loss by three and a half years in the ear which passed unilaterally and 50% by five years in bilateral passes. The data show early and rapid deterioration of hearing in children with cCMV-related SNHL, furthering support for universal newborn screening with close audiological follow-up [42]. Our cohort supports universal screening as 85% of patients with cCMV who passed their NBHS went on to develop SNHL. With half of children with cCMV developing delayed onset hearing loss post a passed NBHS, cCMV screening is essential to improve care and follow-up as this hearing loss may be stabilized or even improved with early evaluation and treatment [33].

4.4. Strengths and limitations

The relatively large size of our study population and participation across multiple sites is a strength of this study. Yet, our study is not without limitations. Errors in documentation as is possible in a retrospective chart review may influence outcomes. Lack of universal screening skews this cohort in favor of symptomatic patients. Limited length of follow up also may contribute to study outcomes and could explain the lack of progression from unilateral to bilateral hearing loss

determined by the study. During systematic chart review, the inability to identify symptoms or characterization of SNHL could have influenced the data. This is represented by almost 68% and 91% of patients with "unknown" presence of IUGR and CMV in CSF respectively. Documentation from outside of NCHS and loss of follow up may introduce inconsistencies in the data.

5. Conclusions

Approximately one half of children with symptomatic cCMV in our cohort developed SNHL related to CMV. This hearing loss progression may manifest as a worsening in severity and/or progression from unilateral to bilateral hearing loss. The majority of children with symptomatic cCMV eventually end up with severe to profound range loss in at least one ear. Children with symptomatic cCMV are at high risk of delayed onset and progressive hearing loss and should be monitored closely.

Ethics approval and consent to participate

This project was approved by the Nemours Institutional Review Board 2 in Jacksonville, FL on 10/15/2019 with study number 1507322-6.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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